Evidence–Based Research of Prolotherapy

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Introduction

Prolotherapy, injection for repair or growth of connective tissue, has a rapidly expanding body of literature, and has potential unique advantages by targeting the primary source of pathology in connective tissue or ligament (degeneration or osis rather than cells). Both literature interpretation and decisions on reimbursement are hampered by the variety of solutions used and the variety of methods used. Nevertheless, there are several areas of solutions used in literature in which the unique advantages of prolotherapy are being demonstrated to the point where reimbursement considerations are beginning to merit discussion and close observation for followup studies. This is particularly true because:

1. Other regenerative methods are far more costly such as:
   a. Surgically based: IE: Endoscopic knee cartilage harvesting, cell expansion and endoscopic grafting, or
   b. Equipment based: IE: Extracorporeal wave therapy and
   2. The efficacy and cost efficiency of prolotherapy per treatment is sufficient enough that a pragmatic approach such as covering a three treatment trial and requesting a 30% improvement in pain or function to consider further coverage is feasible.

Note: that prolotherapy is not the only modality of treatment that cannot be typically therapies that themselves cannot be theoretically covered in a double blind fashion (such as surgery or physical therapy), in the opinion of this reviewer the quality of the studies already completed on use of prolotherapy in the areas summarized generally exceed those for surgery or physical therapy. The references summarized herein are not comprehensive but rather represent the highest quality studies, regardless of outcome. Because there are a variety of injectants and methods in clinical use for prolotherapy, the approach taken in this summary is to recommend that two quality research studies be conducted using the same approach for the same condition with favorable outcome before considering insurance coverage. Those reading this summary may also find a recent review article written by PM&R Specialists from Harvard Medical School, Tufts University School of Medicine and Spaulding Rehabilitation Hospital of particular interest in explaining the concepts and reinforcing the positions taken. (Borg-Stein 09.)

Research Summary By Condition

Achilles tendinosis: Eccentric loading exercises (ELE) are the current standard of care treatment approach. However, randomized comparison to subcutaneous 20% dextrose injection (subcu prolotherapy) has shown a trend toward reduced pain 12 months post procedure, but quickly reached with subcutaneous dextrose alone and significantly better with ELE combined with subcutaneous dextrose injection. (Yelland 09) In another study, nipples were performed on 32 consecutive patients with an average of 26 months of pain with a 25% dextrose injection in the Achilles has shown VISA scores improvement at 12 months post procedure but no long term benefits. Thirty out of 32 patients (94%) were contactable at an average followup of 12 (4.5-28) months after the last treatment. Their average improvement in pain with daily activity was 84% and after sporting activity 78.1%. and controlled ultrasound has demonstrated a high significant p = .0007 decrease (improvement) in the peak ultrasound of the Achilles as well as a significant reduction in Achilles numbers and a reduction in cleft of the ultrasound image. (Nirschl 2008) The main observation of this literature is that a consecutive patient study with high followup percentage and high success at return to sport or with high followup percentage and objective radiographic correction of pathology is a powerful study design.

Both studies, (superficial prolotherapy studied an randomized fashion, and infratendinous prolotherapy studied in consecutive fashion with minimal data loss, long term outcome and objective radiographic measures), are high quality. A followup study reproducing either approach is recommended prior to considering insurance coverage for prolotherapy for Achilles tendinosis.

Achilles laxity: The only study on AXL laxity thus far used a KT–1000 to objectively measure side to side (knee to knee) laxity of the AXL. Intraarticular injection of 12.5 to 25% dextrose every 2 months X 3 and PRN led to elimination of laxity in 10/16 knees by machine measure and an average improvement in pain with weight bearing of 85% subjective swelling of 52% and subjective looseness of 54%. (Reeves 03) Note this study was small as was in patients who also had substantial osteoarthritis but offers an approach to repair of loose AXL that is offered by no other treatment, and is a reproducible and potentially cost effective method (simple intraarticular prolotherapy). However, it is recommended that a large consecutive patient study with machine measure(s) be conducted, along with MRI confirmation of the lack of complete AXL rupture. If a follow up study confirms tightening of the AXL by intraarticular injection in symptomatic patients, insurance coverage of a trial of simple intraarticular injection of proliferant solution for AXL laxity merits consideration.

Finger osteoarthritis: Injection of chronically painful fingers in osteoarthritis with dextrose proliferant has been studied in randomized controlled fashion with best results. (Reeves 00–2) Although this was in knees only and therefore results may not apply to fingers, the results were encouraging and to this day remain the best of any treatment option. Despite this, a followup study comparing long term benefit over the control solution, we do not recommend coverage of prolotherapy for finger arthritis.

Groin Pain: A small consecutive study on 20 consecutive patients with objective radiographic ultrasound measures was published. (Suresh 2006) Dry needling was performed identically to an autologous blood injection. Although only one injection was significant in pain at 10 months post procedure as well as improvement in echogenicity on ultrasound and a decrease in abnormal (ne) blood vessels. 3 patients failed and opted for surgery but in the remaining 17 VAS for pain improved from 8 to 2.2 and Nirschl score from 6 to 1. Hypoechoic change in the flexor tendon significantly decreased between pre–procedure, when there was a mean (DS) of 6.45 (1.47) , and at 10 months, when it was 3.85 (1.37) (p = 0.001). Doppler ultrasound showed that neovascularity decreased between pre–procedure. The measurement of objective improvement changes enhancing the powered effect of this study. A larger study with usual treatment or no injection control is recommended prior to insurance coverage consideration.

Groin Pain: Return of elite athletes to full sport after failure with other methods of treatment, as long as there is avoidance of data dropout and a strict consecutive protocol is a worthwhile outcome. A study of 24 elite level athletes with chronic groin pain of all standard therapies, and failure to play at high level reported in 2005. (Topol 2005) 22/24 returned to full play in sustained fashion, with 22 of them to rugged play (rugby). This study was then in essence repeated with non–elite athletes with identical results, (Topol 2008) 51 were enrolled, completed an average of 2 treatments (average of 3 treatments) and 44/48 returned to full sustained play, with a variety of sports involved. This is remarkable efficacy rate and compares nearly identically to outcome from the best surgically–based studies with many times the expense. This is sufficient evidence to recommend a three treatment trial of prolotherapy in patients with groin pain, although additional studies are recommended in non–elite athletes.

Knee Osteoarthritis: A single randomized controlled trial showed benefit of dextrose injection over simplelidocaine. (Reeves 2000–2) Although this was in knees near or at end stage (3 mm average cartilage and with substantial symptoms), this study has not been reproduced. Prior to consideration of prolotherapy for knee arthritis it is recommended that a second randomized controlled trial be performed or that an arthroscopically based study demonstrate visual proof of cartilage growth in response to the proliferant utilized.

Low Back Pain: Four randomized controlled trials have been performed. (Ongley 87, Klein 93, Dechow 99, Yelland 04). One was egregiously flawed (Dechow 99). Both were performed by 40 elite athletes and yielded mixed results. 20% dextrose injection (subcu prolotherapy) along the area of mid portion tendinosis in the Achilles has shown VISA–A scores at 12 months post procedure of 12/15 to 20/15, with a trend toward significance, and a high return to sport of 85% by athletes. This was with a strong proliferant and naturally led to pain flare in the proliferant group with a worse outcome than the control group. The other three studies demonstrated long term and substantial reductions in disability in both active and control groups, favoring the proliferant group but not with statistical significance. This is because even the control groups were not placebo groups. Repetitive stress is even the outcome effect through several mechanisms. Note that all other consecutive case series of low back pain patients have also confirmed substantial and sustained improvements in pain and function with injection of chronic low back pain patients with chronic low back pain (Bonet 05, Cusi 07). There is no other modality of treatment that has more evidence of long term benefit for low back pain than prolotherapy in such chronic patients. Insurance coverage for low back pain treatment is recommended after another study is published in which a usual treatment control or other non injection control is utilized in the study design to definitively confirm statistically significant improvement in low back pain. It is recommended that the treatment method be clearly described and easily reproducible to allow for clear coverage decisions.

Patellar tendinosis: Two pilot studies have been performed. One used platelet rich plasma with ultrasound guided delivery to areas of tendinosis (Volpi 07) and one used polidocanol with ultrasound guided delivery to areas of neovascularization which is intimately connected to tendinosis. (Alfredson 05) Both were favorable in outcome with excellent pain reduction and improvement in function, although neither emphasized objective followup by ultrasound of changes in neovessels or histology. Prior to coverage consideration a large consecutive patient collection with little or no drop out and long term followup is recommended for either or both of these modalities of treatment.

Plantar fasciosis: There are no regenerative approach alternatives to proliferant injection except extracorporeal shock wave which has a much higher cost. A consecutive patient study of 20 patients with chronic plantar fasciosis treated with dextrose proliferant injection was reported. (Ryan 09). A mean of 3 treatments were given with a good to excellent results in 16/20. A second and larger study using dextrose proliferant with chronic plantar fasciosis with minimal dropout and

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long term outcome with more precise measurement tools will merit attention for coverage consideration.

**Tennis elbow (Lateral or Extensor tendinosis):** A well-designed randomized control trial was published in 2008 in which 24 subjects with chronic elbow pain were assigned to injection with saline or injection with a combination of dextrose and sodium morrhuate. 0, 4 and 8 week injections were performed. (Scarpone 2008) Followup at 16 weeks demonstrated 32% versus 90% improvement, highly significant, favoring the proliferant group. Functional and pain improvement persisted in the proliferant group at 1 year. Another study was reported by Mishra in which 20 surgical candidates were assigned randomly to receive either PRP or bupivicaine injection. Withdrawal of blood in all patients to allow full blinding was not approved by the human subject committee. Injection was only given once, resulting in a VAS improvement for pain at 8 weeks of 16% (bupivicaine) versus 60% (PRP) improvement. At mean followup of 25.6 months 91% improvement in pain was noted. Both studies represent good pilot outcomes and there are other studies reviewed as well in a recent review publication. (Rabago 09). Coverage of a treatment trial may merit consideration given the cost and limited efficacy of other approaches (surgical or non surgical in this condition. However it is recommended that another study be conducted using any of the above methods with larger size comparing usual therapy or non injection control to injection of dextrose or PRP with long term outcome measures.

**Summary**

This has been a brief summary of research findings in common conditions and recommendations for reimbursement. It should be noted that all of the above conditions have been shown at least at pilot study level to be successfully treated with a minimum of treatment which would represent considerable cost efficacy. Although insurance reimbursement is recommended only for groin pain at this time, in most areas discussed only one additional high quality study is needed to recommend consideration of insurance coverage.

Reimbursement methods are problematic. It is recommended that at this time that insurance coverage be made according to treatment time at a rate of $400 per hour for non sedation procedures and $600 per hour for treatments that require sedation. The patient would need to pay in addition for proprietary components of treatment (IE PRP) that are not included in usual proliferant injection.

**References in Order of Citation**


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